

### **REMARKS/ARGUMENTS**

The specification stands objected to with regard to the priority claim. As amended, the priority claim recites the present status of the U.S. Patent Applications Serial No. 09/355,014 and Serial No. 09/012,116.

The amendments to Claims 124 and 133 find support in the specification and claims as originally filed. Support for the phrase "within the hinge region" may be found in the specification, for example, at page 50, lines 20-28, at lines 20-22 in particular, and elsewhere in the specification.

Support for the new claims may be found in the specification and claims as originally filed; for example, at pages 42-43, particularly page 43 lines 2 and 8; at page 48, lines 3-9; page 50, lines 20-28, and elsewhere in the specification and claims as originally filed. Applicants believe the new claims to be directed to allowable subject matter.

No new matter is added by way of the amendments to the specification or by way of the claim amendments or new claims.

Applicants acknowledge the withdrawal of the rejections to Claims 124-132 under the judicially created doctrine of obviousness-type double patenting; and of Claims 124-130 under 35 U.S.C. §103(a) as allegedly obvious over several references cited by the Examiner.

With this amendment, claims 124-145 are pending in the application. Claims 124-133 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement (the Examiner noting that this is a "new matter" rejection), and under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Applicants respectfully traverse these rejections.

#### **The Rejections Under 35 U.S.C. §112, First Paragraph**

Claims 124-133 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner has characterized the rejection as a "new matter rejection" and has also suggested that he believes that Claims 124-133 are not enabled by the specification.

#### **The "New Matter" Rejection**

Claims 124-133 stand rejected as allegedly not supported by the specification, the Examiner suggesting that "there is no support for the combination of a polymer in a cysteine in

the hinge and substitution in the heavy or light chain as broadly claimed" (paragraph 15, page 7, lines 2-3 of the Office action dated May 6, 2005). Applicants disagree with this characterization of the disclosure (drawing the Examiner's attention, for example, to pages 51 *et seq.* in the specification). However, the question of whether or not there may be support "for the combination of a polymer in a cysteine in the hinge and substitution in the heavy or light chain" is believed to be moot, as the present claims are directed to:

A conjugate ... [having] one or two nonproteinaceous polymer molecules at a free sulfhydryl group of a cysteine residue within the hinge region ... wherein a disulfide bridge within the hinge region is avoided by substituting another amino acid for the corresponding cysteine residue within the hinge region in the opposite chain ...

Thus, the cysteine substitution in the claimed conjugate is explicitly within the hinge region so that the claim is not directed to "substitution in the heavy or light chain as broadly claimed" as suggested by the Examiner in his remarks regarding the rejection. The claims not being directed to the allegedly "new" subject matter, Applicants believe that the rejections of Claims 124-133 under 35 U.S.C. §112, first paragraph, for allegedly containing new matter are overcome.

#### The "Enablement" Rejection

The Examiner has further suggested that Claims 124-133 are somehow not enabled, and would require undue experimentation, for example, to "avoid specific conjugation to the hinge and not the free cysteine in the heavy or light chain" (pages 8-9 of the Office action dated May 6, 2005).

In this regard, Applicants acknowledge the Examiner's statement that the specification is "enabling for an antibody fragment that is modified by one or two PEG molecules at a free cysteine residue within the hinge, wherein the apparent molecular weight on size exclusion chromatography is about 500 or 800 or 1800 kD and has an average PEG of 20 or 30 kD and the conjugate is apparently 8 fold greater than the parent fragment where in [sic] the conjugate binds an antigen which can be HER2 or CD20."

As discussed above, the present claims are not directed to substitution of a cysteine in the heavy or light chain. The pending claims are directed to antibody fragments modified by one or two PEG molecules at a free cysteine residue within the hinge. Accordingly, Applicants respectfully submit that Claims 124-133 are directed to subject matter acknowledged by the

Examiner to be enabled. Accordingly, Applicants respectfully submit that rejections of Claims 124-133 under 35 U.S.C. §112, first paragraph, for allegedly failing to comply with the written description requirement are overcome.

### **The Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 124-133 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. The Examiner suggests that Claims 124-133 "are indefinite for reciting 'wherein a disulfide bridge is avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain,' asking "[i]s the disulfide bridge avoided in the hinge or in some other part of the molecule such as the heavy and light chain or somewhere else?" (page 5, paragraph 13, lines 4-8 of the paragraph).

However, as amended, the claims recite that the disulfide bridge is avoided within the hinge region. For example, Claim 124 recites "wherein a disulfide bridge within the hinge region is avoided by substituting another amino acid for the corresponding cysteine residue within the hinge region in the opposite chain of said antibody fragment " and Claim 133 recites "wherein a disulfide bridge within the hinge region is avoided by substituting another amino acid for the corresponding cysteine residue within the hinge region in the opposite chain of said antibody fragment." Thus, the claims distinctly and particularly stating that the disulfide bridge within the hinge region is avoided by the recited substitution, Applicants submit that the claims are not indefinite.

Accordingly, Applicants respectfully submit that the rejections of Claims 124-133 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention are overcome.

### **CONCLUSION**

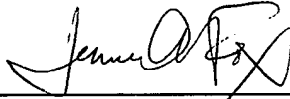
In conclusion, Applicants respectfully submit that all claims are in condition for allowance, and request reconsideration and allowance of all pending claims.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Please charge any fees, including fees for extension of time, or credit overpayment to  
Deposit Account No. 08-1641, referencing Attorney's Docket No. 39766-0092 A.

Respectfully submitted,

Date: June 15, 2005

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